Head and thorax elevation during active compression decompression cardiopulmonary resuscitation with an impedance threshold device improves cerebral perfusion in a swine model of prolonged cardiac arrest

A Thesis

SUBMITTED TO THE FACULTY OF THE
UNIVERSITY OF MINNESOTA
BY

Johanna Catherine Moore

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTER OF SCIENCE

Advisor: Michelle H Biros, MD

October 2017

ACKNOWLEDGEMENTS

Dr. Moore would like to acknowledge her co-investigators on this project:

Nicolas Segal MD PhD

Michael C Lick BA

Kenneth W Dodd MD

Bayert J Salverda BA

Mason B Hinke BA

Aaron E Robinson MD MPH

Guillaume Debaty MD PhD

Keith G Lurie MD

ABSTRACT

Aim: To compare brain blood flow between the head up (HUP) and supine (SUP) body positions during prolonged cardiopulmonary resuscitation (CPR), using active compression-decompression (ACD) CPR and an impedance threshold device (ITD) in a swine model of cardiac arrest.

Methods: After 8 minutes of untreated ventricular fibrillation (VF), followed by 2 minutes of ACD-CPR+ITD in the SUP position, pigs were randomized to 18 minutes of ACD-CPR+ITD in either 30^{o} HUP or SUP position. Microspheres were injected before VF, and then 5 and 15 minutes after study start.

Results: Brain Blood flow (ml/min/g, mean ± SD) after 15 minutes of CPR was 0.42±0.05 for HUP (n=8) and 0.21±0.04 for SUP (n=10), ($p<0.01$). The HUP group also had lower intracranial pressures and higher cerebral perfusion pressures.

Conclusions: Brain blood flow in the HUP position was higher in than the SUP position. This provides pre-clinical support to proceed with a clinical evaluation of head up CPR in humans.

Table of Contents

List of Tables

List of Figures

1. Introduction

The head up (HUP) position during cardiopulmonary resuscitation (CPR), either with a whole body tilt, or elevation of just the head and thorax, has been described as a novel approach to increase cerebral perfusion pressure when compared with CPR in the supine position (SUP) in swine models of cardiac arrest.[1-4] Additionally, higher cerebral blood flow has been described with the head up whole body tilt versus whole body flat after 5 minutes of mechanical CPR with an impedance threshold device (ITD). [1] However, most clinical CPR efforts last a minimum of 15-20 minutes.[5] This poses a potential risk of HUP CPR when using a whole-body tilt approach since blood flow to the brain would be anticipated to decrease over time secondary to pooling of blood in the lower extremities. This physiology is known from the use of head-up tilt-table testing to induce syncope. [6, 7] To reduce this potential risk, we previously developed a HUP device that elevates just the head and upper thorax and demonstrated higher cerebral perfusion pressure (CerPP) in the HUP position over a period of 22 minutes with active compression decompression (ACD) + ITD CPR. [2] With this device the head is elevated about 25 cm and the heart about 5 cm relative to the rest of the body. Building on these studies, in the current investigation we tested the hypothesis cerebral blood flow would be higher with HUP versus SUP during prolonged ACD CPR + ITD. [2] The primary endpoint of this study was brain blood flow after 15 minutes of CPR in a porcine model of ventricular fibrillation (VF) cardiac arrest. Secondary endpoints included brain blood flow after 5 minutes of CPR, systemic hemodynamics including intracranial pressure, and end tidal CO2 (ETCO2) for up to 20 minutes of CPR.

2. Materials and Methods

Study Ethics

This study was approved by the Institutional Animal Care and Use Committee of the Minneapolis Medical Research Foundation (MMRF). Animal care was compliant with the National Research Council's 1996 Guidelines for the Care and Use of Laboratory Animals, and a certified and licensed veterinarian assured protocol performance was in compliance with these guidelines.

Study Design and Measurements

Techniques describing the surgical preparation, anesthesia, microsphere techniques, and data monitoring and recording used in this study have been previously described. [1, 2] Female Yorkshire farm pigs weighing 36-44 kg were fasted overnight after acclimatizing in the animal care facility for three days. Intramuscular ketamine (10 mL of 100 mg/mL) was administered in the holding pen. Animals were transferred to the surgical suite where they were treated with inhaled isoflurane at 1% to 2.5%, then intubated with a 7.5 French endotracheal tube and ventilation was performed using a ventilator (Narkomed, North American Dräger, Telford, PA) with tidal volume 10 mL/kg. ETCO2 and oxygen saturation were recorded with a CO2SMO Plus® (Novametrix Systems, Wallingford, CT). The respiratory rate and FiO2 were adjusted to keep oxygen saturation above 92% and ETCO2 between 37 and 43 mmHg. Intravenous access was obtained.. All animals received a normal saline bolus of 1000 ml during preparatory phase to maintain the mean right atrial pressure between 4 and 7 mmHg.

Temperature was monitored with an esophageal probe, and maintained between 36.5 and 38.5°C Proximal airway pressure, a surrogate for intrathoracic pressure, was measured with a differential pressure transducer (TSD160C, BioPac Systems, Inc., Goleta, CA). [8] Central aortic blood pressures were measured with a micromanometer-tipped catheter (Mikro-Tip Transducer, Millar Instruments, Houston, TX) placed through the right femoral artery into the descending thoracic aorta to the level of the diaphragm. A similar Millar catheter was placed in the right femoral vein and advanced to the right atrium (RA) to measure right atrial pressure. A pigtail catheter was positioned in the left ventricle (LV) under fluoroscopic guidance via the left femoral artery. This was used for microsphere injections (see below). The position of all vascular micromanometer-tipped catheters was confirmed by fluoroscopy before induction of VF. Intracranial pressure (ICP) was measured via a burr hole in the skull, and insertion of a Millar catheter into brain as previously described. [1] All animals received a 100 units/kg bolus of heparin intravenously every hour.

Data, including electrocardiographic monitoring, aortic pressure, RA pressure, LV pressure, ICP, and ETCO2, was continuously recorded using the BioPac computer system (BioPac; BioPac Systems Inc., Goleta CA). All data was stored using the BioPac computer data analysis program. Arterial blood gases (ABG) were acquired through the femoral artery catheter and analyzed with a Gem Premier 3000 device (Instrumentation Laboratory, Lexington, MA).

When the preparatory phase was complete, isoflurane was discontinued, and after 3 minutes VF was induced with delivery of direct electrical current from a pacing wire placed in the right ventricle. ACD CPR + ITD was performed with an automatic piston

device (Pneumatic Compression Controller; Ambu International, Glostrup, Denmark) as described previously. [2, 9] ACD CPR was performed at a rate of 80 compressions/min, with a 50% duty cycle and depth of 22.5% of antero-posterior chest diameter, and the chest was pulled upwards after each compression with a suction cup on the skin at a decompression force of approximately 10 kg. An ITD, (ResQPOD-16, Zoll Medical, Minneapolis, MN) was placed at the end of the endotracheal tube. The HUP CPR device used elevated just the head and shoulders and upper thorax 30º, as previously described.[2] While transitioning from supine to the HUP CPR was performed in an uninterrupted manner. During CPR, positive pressure ventilation was delivered with oxygen, titrated to a SpO2 of ≥92%, with a tidal volume of 10 mL/kg. If the animal was noted to gasp during the resuscitation, time at first gasp was recorded. Succinylcholine was administered at a dose of 3mg (0.075/kg) to inhibit gasping after the third gasp.

Microsphere protocol

Blood flow to the heart, brain, kidney, and liver was measured with microsphere injection into the LV under stable baseline conditions 5 min prior to the induction of VF. Neutron activated microspheres (STERIspheres™, BioPAL™: BioPhysics Assay Laboratory, Worcester, MA) 15 microns in diameter containing Samarium (152Sm), Ytterbium (175Yb) and Lutetium (177Lu) were used.

The number of microspheres needed per injection (μ) was determined as follows: $\mu = 1.2 \times 106 + ((1.9 \times 105) \times \omega)$ where μ is the number of microspheres and ω is the weight of the pig. Then, the volume of microspheres injected at baseline was calculated as follows

$$\text{Volume} = \frac{\mu}{((5 \times 108)/20).}$$

A higher number of microspheres was injected during CPR compared to baseline to account for the low flow state of CPR.[10] Immediately after microsphere injections, reference blood samples were withdrawn continuously over 4 minutes from the descending aorta at a collection rate of 10 ml min^{-1}.[1, 10]

At the end of the study, animals were sacrificed and then tissue samples from the brain (posterior [pons portion of the brain-stem, hippocampus], left and right cortex), the heart (free left ventricle wall, apex, papillary muscle, and septum), the kidney (cortex), and the liver were obtained. Tissue and blood samples were desiccated and sent to the reference BioPhysics Assay Laboratory for analysis.[10]

Organ blood flow could then be calculated in the reference laboratory after performing neutron activation and calculating how many microspheres are in the tissue and reference blood samples by using the following equation:

$$\text{Organ flow (mL/min)} = \frac{\text{Known organ flow (mL/min)} \times \text{No. of microspheres in organ with unknown flow}}{\text{No. of microspheres in organ with known flow}}$$

Here, the known organ flows were from the reference blood samples, and the number of microspheres in the organ with unknown flow calculated in each organ by neutron activation. Therefore, the blood flow to each organ could then be calculated in mL/mg/g tissue.[11]

Experimental Protocol

The experimental protocol is outlined in Figure 1. After 8 minutes of untreated VF, ACD CPR + ITD was performed with a 30:2 compression: ventilation ratio, and positive pressure ventilation with room air was provided while all pigs were in the SUP to simulate basic life support (BLS).[12] After 2 minutes of CPR, animals were randomized either HUP CPR or SUP CPR and continuous asynchronous ACD CPR+ITD CPR was continued for 18 minutes with a 10:1 compression: ventilation ratio to simulate advanced life support (ALS).[13] Randomization was performed with block randomization in groups of 4 prior to the study start. All members of the research study team were unaware of the randomization until 1 minute into CPR, when an unmarked envelope was opened with the randomized body position. . Microsphere injections were performed after 5 and 15 minutes of CPR and 20 ml of blood were collected over 4 minutes (see above). After 19 total minutes of CPR, 0.5 mg of adrenaline was administered intravenously followed by 25 mg of amiodarone. One minute later, pigs were defibrillated with up to three 200 J biphasic shocks (X-series, Zoll Medical, Chelmsford MA). If return of spontaneous circulation (ROSC) was not obtained, CPR was resumed and a shock was delivered every 2 minutes together with 0.5 mg of adrenaline every 4 minutes. If spontaneous circulation was not restored after a total of 3 shocks, CPR was stopped. If ROSC was obtained, animals were euthanized with an intravenous injection of KCl 20 minutes later.

2.3 Data Analysis

The sample size calculation was based on previous studies. We estimated the brain blood flow would be approximately 25% higher in the HUP ACD CPR + ITD

group. [1] Assuming an alpha level of 0.05 and 80% power, 11 animals were needed per group to detect an 80% difference.

Hemodynamic data were analyzed at baseline just prior to the microsphere injection, and then after 5, 15, 19, and 20 minutes of CPR. Airway, aortic, right atrial, and intracranial pressures measurements were made from 3 sequential compression-decompression cycles between positive pressure breaths. These values were averaged for each of the compression-decompression cycle measurements for each time point in each animal study. The coronary perfusion pressure (CPP) was calculated as the difference between the decompression phase aortic and right atrial pressures, and represents the aortic to right atrial pressure gradient during the relaxation phase of cardiopulmonary resuscitation. As with previous studies, our target CPP during CPR was at a minimum of 15 mmHg since CPP of at least 15-20 correlates with ROSC in animals and humans, and is a marker of high quality CPR.[14, 15] In addition, when calculating the mean CerPP we used the mathematical difference between aortic and intracranial pressure over a 15 second interval at each time point.

Data are expressed as mean ± standard deviation (SD). Statistical analysis was performed using SPSS 21 (IBM Corporation, USA). An unpaired Student's t-test was used to determine significance between HUP and SUP for the primary outcome of blood flow at 15 minutes, and also for secondary hemodynamic outcomes. A Fisher's exact test was used to compare ROSC rate. All statistical tests were two-sided, and a p value of less than 0.05 was required to reject the null hypothesis. Unadjusted p values are presented for the secondary analyses. Studies where technical difficulties were encountered due to either dislodgment of the left ventricular catheter, or inability to

compress the chest 22.5% of the antero-posterior diameter, did not meet study inclusion criteria and were therefore not included in the results.

3. Results

Eighteen pigs weighing 39.5 ± 8.2 kg randomized to CPR in HUP (n=8) or SUP (n=10) met study inclusion criteria. Results showing the blood flow to the brain, heart, kidney, and liver before VF and then 5 and 15 minutes after the start of CPR are provided in Table 1 and Figure 2. The blood flow to the brain after 15 minutes of CPR, the primary study endpoint, was higher in the HUP group at 0.42 ±0.05 ml/min/g versus 0.21 ± 0.04 in the SUP group, respectively ($p<0.01$). When compared with pre-VF values, blood flow to the brain after 15 minutes of CPR was 25% of baseline in the SUP versus 50% in the HUP. Regional brain blood flow before cardiac arrest and after 5 and 15 minutes of HUP and SUP CPR are shown in Figure 2.

Key hemodynamic variables for the two treatment groups are shown in Table 2. Pigs treated with HUP CPR had significantly lower intracranial pressure (ICP) and higher CerPP after 5, 15, 19, and 20 minutes of ACD CPR + ITD versus SUP. One minute after adrenaline, the CerPP values remained higher in the HUP group. The time to first gasp was 282 ± 51 seconds in the HUP group versus 437 ± 185 seconds in the SUP group ($p=0.045$).

The ROSC rate and ABG values were similar between the two treatment groups. With HUP CPR 5/8 pigs achieved ROSC versus 3/10 in the SUP group ($p=0.34$). The arterial blood gases were similar at baseline and in the animals that had ROSC, as shown in Table 3.

Discussion

The evaluation of any new approach in the treatment of patients in cardiac arrest requires preclinical proof of safety and effectiveness. This translational process is ongoing in regard to the potential benefits of elevating the head and thorax during CPR. Building upon recent studies demonstrating proof-of-concept of HUP CPR in multiple animal laboratories,[1, 2, 16] the current study was designed to determine if elevation of the head and thorax was effective, safe, and consistent with previous work during a prolonged CPR effort in pigs. The experimental protocol lasted 20 minutes, the average duration of many CPR efforts. Two questions were assessed in this protocol: are the beneficial physiological effects of HUP CPR sustained over time and can this new approach be safely applied in a prolonged resuscitation? ACD CPR + ITD was used based upon prior animal studies demonstrating that conventional CPR did not provide enough forward flow to pump blood "uphill" to the brain during HUP CPR, whereas a longer-term hemodynamic benefit was observed with HUP ACD+ITD CPR. [2]

These results show for the first time that blood flow can be maintained at levels of 50% of baseline values in this animal model of prolonged CPR. By contrast, ACD CPR + ITD in the flat position provided only 25% of normal brain flow after 8 minutes of untreated VF and 15 minutes of CPR. The microsphere blood flow studies parallel the hemodynamics findings of higher CerPP throughout the resuscitation effort, and results from the current study confirmed prior hemodynamic studies. Two hemodynamic factors contributed to the higher and sustained CerPP in the HUP group; a gradual reduction in ICP in the HUP group over time and a sustained mean aortic pressure. By comparison, ICP remained relatively high and constant and aortic pressure relative low and constant in

the SUP group. An earlier study demonstrated a similar improvement in CerPP, but such measurements are calculated by the difference between the arterial driving pressures and the resistance generated by ICP. This calculated CerPP has the potential to overestimate the actual delivery of blood to brain tissues as the arterial pressure cannot be easily measured in the cerebral arteries, due to technical limitations. [2] This limitation of the previous work highlighted the need to also demonstrate increased brain blood flow with HUP CPR in a prolonged CPR effort as shown in the current study.

Blood flow to the brain is needed to preserve and maintain brain function. Gasping is also dependent upon brain blood flow. [17] Pigs treated with HUP CPR took their first spontaneous gasp earlier compared with the SUP group. This may be of clinical significance as gasping is associated with brain stem functionality and better clinical outcomes in patients in cardiac arrest. As such, time to first gasp may be a useful clinical endpoint when evaluating HUP CPR in human patients. [17-21]

The increase in brain blood flow and shorter time to first gasp are a direct result of HUP CPR. These observations are most likely due to the multiple effects of gravity and ACD CPR + ITD on intracranial and right heart pressures and trans-pulmonary blood flow. [1-3] With HUP CPR, venous blood flow to the thorax and right heart is enhanced from the brain and paravertebral plexus; this decreases ICP and increases cardiac preload. [1-3, 22] This reduction in ICP lowers resistance to forward brain flow. The reduction in ICP and right-sided venous pressures in combination with the factor of pumping blood "uphill" with compression during HUP CPR also reduces the concussive forces that simultaneously strike the brain with each chest compression from a combination of simultaneous high arterial and venous high pressure waves. In these recent studies ACD

CPR + ITD was used to generate high enough aortic pressures to overcome the challenge of pumping arterial blood "uphill".[2] Without the ITD there was less of a clinically meaningful benefit with HUP CPR. [1]

Previous studies have demonstrated that ACD CPR + ITD is superior to conventional CPR in terms of blood pressure, brain flow to the heart and brain, and long-term survival with favorable neurological function. [3, 5, 23] In this study, ACD CPR + ITD in both positions resulted in similar aortic pressures and ABGs. Right atrial pressures tended to be lower in the HUP group but these differences were not significant. The current study suggests that when ACD CPR + ITD is performed continuously, first SUP, during the transition from SUP to HUP, and then HUP for a prolonged period of time, there is no increased risk of harm.

The current study provides additional support for the concept of HUP CPR but does have some limitations. First, this study is in an animal model of VF cardiac arrest, using young healthy swine without cardiac disease. The current VF model is widely used in cardiac arrest research, however may not necessarily translate to humans. Additionally, many prolonged arrests have an initial presenting rhythm of pulseless electrical activity (PEA), or asystole. However, the VF prolonged arrest model is commonly used.[24-27] While this study provides definitive evidence of an increase in blood flow to the brain during prolonged HUP CPR, it is unknown if this benefit will translate into an increase in long-term survival with favorable brain function. Further study is needed in this regard. Another limitation is that given the higher than anticipated effect size we stopped randomizing and performing studies on pigs after 18 pigs. Different from the first study that was used to estimate the sample size[1], in the current study we used an ACD CPR that

pulled upwards with 10 kg versus 1.5 kg, and we only elevated the head and thorax rather than whole body head up tilt. Finally, we did not examine the potential risks and harm of maintaining HUP in pigs in cardiac arrest without ongoing CPR. We suspect that long pauses during cardiac arrest could be potentially harmful in the HUP due to pooling of blood in the abdomen and lower extremities without ongoing circulatory effort.

4. Conclusion

After prolonged ACD CPR + ITD with elevation of the thorax and head, blood flow of the brain was 2-fold higher versus controls treated with the same method of CPR in the supine position. These findings provide additional strong pre-clinical support to proceed with a clinical evaluation of elevation of the head and thorax during ACD CPR + ITD in humans in cardiac arrest.

ml/min/g	Baseline		5 min CPR		15 min CPR	
	SUP	**HUP**	**SUP**	**HUP**	**SUP**	**HUP**
n	10	8	10	8	10	8
Brain	0.84 ± 0.17	0.86 ± 0.14	0.33 ± 0.06	0.45 ±0.07	0.21 ± 0.04	0.42 ± 0.05 *
Heart	1.37 ± 0.19	1.57 ± 0.17	0.51 ± 0.11	0.42 ± 0.09	0.33 ± 0.12	0.34 ± 0.06
Kidney	2.51 ± 0.29	2.32 ± 0.24	0.28 ± 0.08	0.38 ±0.07	0.21 ± 0.06	0.31 ± 0.07
Liver	0.59 ± 0.11	0.76 ± 0.23	0.10 ± 0.02	0.08 ± 0.02	0.05 ± 0.02	0.08 ± 0.02

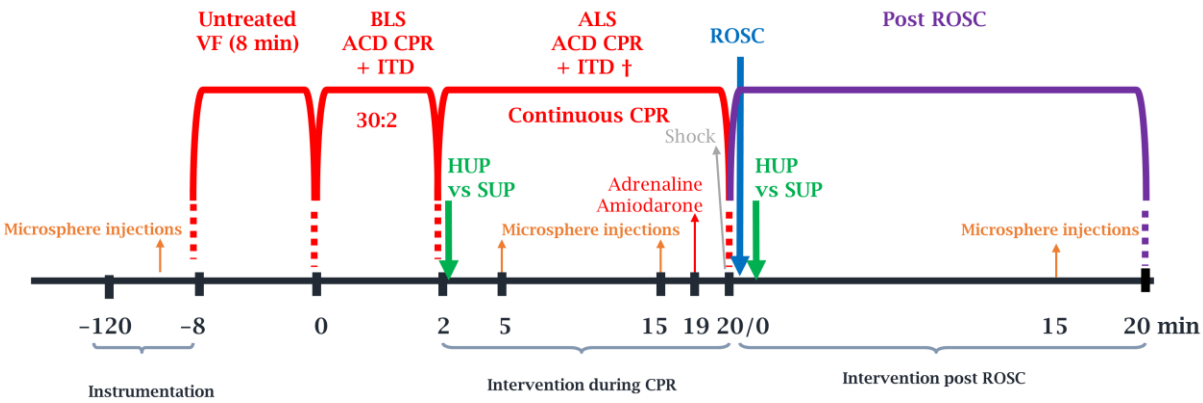
Table 1: Blood flow (ml/min/g) to various organs during cardiopulmonary resuscitation (CPR) in animals randomized to head and thorax elevation (HUP) or supine (SUP) positions. Values are presented as mean ± standard deviation; *p=0.01 compared to the 15 min SUP CPR value.

N SUP=10 HUP=8	**Baseline**		**5 min CPR**		**15 min CPR**		**19 min CPR**		**20 min CPR**	
	SUP	**HUP**	**SUP**	**HUP**	**SUP**	**HUP**	**SUP**	**HUP**	**SUP**	**HUP**
ITP diastole	2.3 ± 1.2	2.0 ± 0.6	-5.3 ± 3.0	-5.8 ± 1.8	-5.7 ± 2.8	-6.0 ± 0.8	-5.6 ± 3.4	-5.1 ± 1.5	-5.1 ± 3.9	-5.4 ± 1.3
Ao systole /diastole	96 ± 12 / 73 ± 10	86 ± 14 / 65 ± 13	56 ± 11 / 24 ± 5	58 ± 10 / 24 ± 5	53 ± 14 / 21 ± 6	59 ± 8 / 23 ± 4	45 ± 17 / 16 ± 8	53 ± 9 / 20 ± 5	52 ± 22 / 21 ± 12	58 ± 13 / 23 ± 7
RA systole/ diastole	7.4 ± 2.2 / 5.9 ± 2.3	7.1 ± 1.9 /5.1 ± 1.7	60 ± 17 / 6.1± 4.9	49 ± 16 / 2.8 ± 3.6	52 ± 15 / 5.7 ± 4.2	48 ± 14 / 2.7 ± 3.4	48 ± 14 / 5.1 ± 4.5	43 ± 14 / 2.0 ± 3.7	51 ± 11 6 / 6±	46 ± 16 / 4 ± 5
ICP mean	18.8 ± 2.5	16.8 ± 3.6	18.3 ± 6.4	10.0 ± 7.0 *	17.7 ± 5.5	7.7 ± 5.5 ***	15.7 ± 4.2	6.1 ± 5.1 ***	14 ± 2	2 ± 2 ***
CPP diastole	66 ± 10	58 ± 13	18 ± 8	21 ± 6	15 ± 8	20 ± 5	11 ± 11	18 ± 6	15 ± 15	20 ± 6
CerPP mean	65 ± 11	60 ± 14	13 ± 7	26 ± 7 ***	11 ± 9	28 ± 5 ***	8 ± 10	27 ± 5 ***	6 ± 11	20 ± 7 **
$EtCO_2$ mean	42 ± 2	42 ± 2	34 ± 16	40 ± 6	28 ± 15	32 ± 14	24 ± 11	28 ± 12	23 ± 10	26 ± 11

Table 2: Hemodynamic measurements in animals randomized to the head up (HUP) or supine (SUP) position during a prolonged cardiopulmonary resuscitation (CPR) effort. Values are presented as mean ± standard deviation. Abbreviations: Intrathoracic pressure (ITP), Aortic pressure (Ao), right atrial pressure (RA), intracranial pressure (ICP), Coronary Perfusion Pressure (CPP), Cerebral Perfusion Pressure (CerPP), end-tidal CO2 (ETCO2), active compression decompression (ACD), impedance threshold device (ITD), *** $p \leq 0.001$; ** $p < 0.01$; * $p < 0.05$, compared to the SUP CPR value at the same CPR time point.

	Baseline		ROSC	
	SUP	**HUP**	**SUP (n-3)**	**HUP (n=4)**
pH	7.46 ± 0.02	7.46 ± 0.03	7.02 ± 0.03	6.97 ± 0.03
PaCO2	42 ± 3	44 ± 1	57 ± 5	73 ± 21
PaO2	85 ± 10	93 ± 16	80 ± 10	91 ± 18
HCO^{3-}	30 ± 2	30 ± 1	15 ± 1	16 ± 4
BE	6 ± 3	6 ± 1	-16 ± 1	-10 ± 4
SaO2	96 ± 2	97 ± 1	86 ± 5	83 ± 11

Table 3: Arterial blood gases results of the head up (HUP) and supine (SUP) cardiopulmonary resuscitation (CPR) groups. Values are presented as means ± standard deviation; Abbreviations: Return of spontaneous circulation (ROSC), base excess (BE)



† **SC:** succinylcholine (0.20 mg/kg IV bolus if gasp >3 in 30s)

Figure 1: Study timeline. Abbreviations: Head Up CPR (HUP), supine (SUP), active compression decompression (ACD) plus impedance threshold device (ITD) cardiopulmonary resuscitation (CPR), ventricular fibrillation (VF), basic life support (BLS), advanced life support (ALS), return of spontaneous circulation (ROSC), adrenaline.

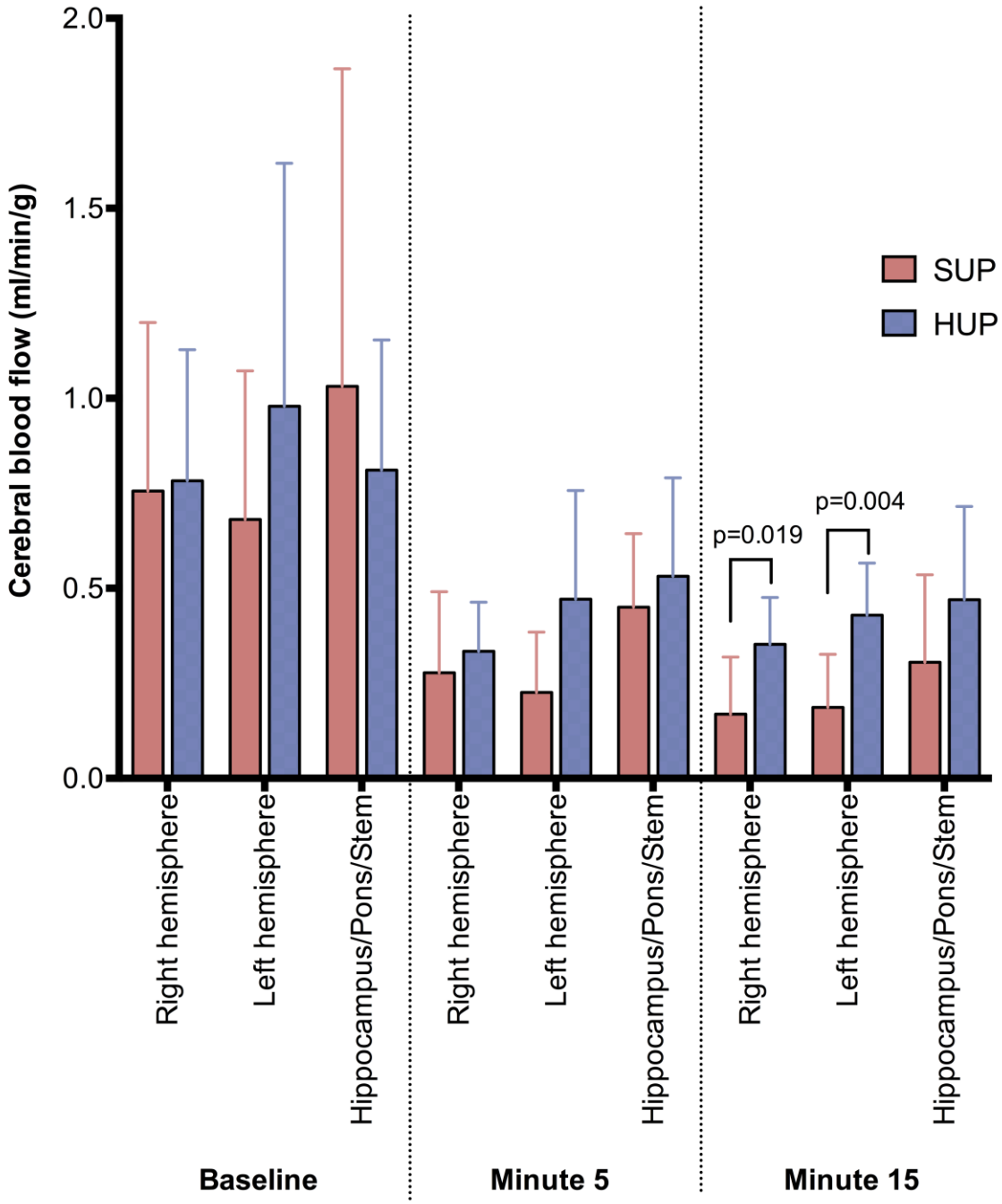


Figure 2: Blood flow to the various areas of the brain with head up (HUP) and supine (SUP) cardiopulmonary resuscitation (CPR)

Bibliography

1. Debaty G, Shin SD, Metzger A, Kim T, Ryu HH, Rees J, McKnite S, Matsuura T, Lick M, Yannopoulos D, Lurie K. Tilting for perfusion: Head-up position during cardiopulmonary resuscitation improves brain flow in a porcine model of cardiac arrest. *Resuscitation*. 2015;87:38-43
2. Ryu HH, Moore JC, Yannopoulos D, Lick M, McKnite S, Shin SD, Kim TY, Metzger A, Rees J, Tsangaris A, Debaty G, Lurie KG. The effect of head up cardiopulmonary resuscitation on cerebral and systemic hemodynamics. *Resuscitation*. 2016;102:29-34
3. Lurie KG, Nemergut EC, Yannopoulos D, Sweeney M. The physiology of cardiopulmonary resuscitation. *Anesth Analg*. 2016;122:767-783
4. Kim T, Shin SD, Song KJ, Park YJ, Ryu HH, Debaty G, Lurie K, Hong KJ. The effect of resuscitation position on cerebral and coronary perfusion pressure during mechanical cardiopulmonary resuscitation in porcine cardiac arrest model. *Resuscitation*. 2017;113:101-107
5. Aufderheide TP, Frascone RJ, Wayne MA, Mahoney BD, Swor RA, Domeier RM, Olinger ML, Holcomb RG, Tupper DE, Yannopoulos D, Lurie KG. Standard cardiopulmonary resuscitation versus active compression-decompression cardiopulmonary resuscitation with augmentation of negative intrathoracic pressure for out-of-hospital cardiac arrest: A randomised trial. *Lancet*. 2011;377:301-311
6. Samniah N, Sakaguchi S, Ermis C, Lurie KG, Benditt DG. Transient modification of baroreceptor response during tilt-induced vasovagal syncope. *Europace*. 2004;6:48-54
7. Lamarre-Cliche M, Cusson J. The fainting patient: Value of the head-upright tilt-table test in adult patients with orthostatic intolerance. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2001;164:372-376
8. Kwon Y, Debaty G, Puertas L, Metzger A, Rees J, McKnite S, Yannopoulos D, Lurie K. Effect of regulating airway pressure on intrathoracic pressure and vital organ perfusion pressure during cardiopulmonary resuscitation: A non-randomized interventional cross-over study. *Scandinavian journal of trauma, resuscitation and emergency medicine*. 2015;23:83
9. Lurie KG, Coffeen P, Shultz J, McKnite S, Detloff B, Mulligan K. Improving active compression-decompression cardiopulmonary resuscitation with an inspiratory impedance valve. *Circulation*. 1995;91:1629-1632
10. Reinhardt CP, Dalhberg S, Tries MA, Marcel R, Leppo JA. Stable labeled microspheres to measure perfusion: Validation of a neutron activation assay technique. *Am J Physiol Heart Circ Physiol*. 2001;280:H108-116
11. Heymann MA, Payne BD, Hoffman JI, Rudolph AM. Blood flow measurements with radionuclide-labeled particles. *Prog Cardiovasc Dis*. 1977;20:55-79
12. Kleinman ME, Brennan EE, Goldberger ZD, Swor RA, Terry M, Bobrow BJ, Gazmuri RJ, Travers AH, Rea T. Part 5: Adult basic life support and cardiopulmonary resuscitation quality: 2015 american heart association guidelines

update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S414-435
13. Link MS, Berkow LC, Kudenchuk PJ, Halperin HR, Hess EP, Moitra VK, Neumar RW, O'Neil BJ, Paxton JH, Silvers SM, White RD, Yannopoulos D, Donnino MW. Part 7: Adult advanced cardiovascular life support: 2015 american heart association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. 2015;132:S444-464
14. Kern KB, Ewy GA, Voorhees WD, Babbs CF, Tacker WA. Myocardial perfusion pressure: A predictor of 24-hour survival during prolonged cardiac arrest in dogs. *Resuscitation*. 1988;16:241-250
15. Paradis NA, Martin GB, Rivers EP, Goetting MG, Appleton TJ, Feingold M, Nowak RM. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. *JAMA*. 1990;263:1106-1113
16. Kim T, Shin SD, Song KJ, Park YJ, Ryu HH, Debaty G, Lurie K, Hong KJ. The effect of resuscitation position on cerebral and coronary perfusion pressure during mechanical cardiopulmonary resuscitation in porcine cardiac arrest model. *Resuscitation*. 2017
17. Bobrow BJ, Zuercher M, Ewy GA, Clark L, Chikani V, Donahue D, Sanders AB, Hilwig RW, Berg RA, Kern KB. Gasping during cardiac arrest in humans is frequent and associated with improved survival. *Circulation*. 2008;118:2550-2554
18. Zhao L, Li C, Liu B, Wang M, Shao R, Fang Y. The association of gasping and outcome, in out of hospital cardiac arrest: A systematic review and meta-analysis. *Resuscitation*. 2015;97:7-12
19. Roppolo LP, Pepe PE, Bobrow BJ. The role of gasping in resuscitation. 2010:83-95
20. Debaty G, Labarere J, Frascone RJ, Wayne MA, Swor RA, Mahoney BD, Domeier RM, Olinger ML, O'Neil BJ, Yannopoulos D, Aufderheide TP, Lurie KG. Long-term prognostic value of gasping during out-of-hospital cardiac arrest. *J Am Coll Cardiol*. 2017;70:1467-1476
21. Sugiyama A, Duval S, Nakamura Y, Yoshihara K, Yannopoulos D. Impedance threshold device combined with high-quality cardiopulmonary resuscitation improves survival with favorable neurological function after witnessed out-of-hospital cardiac arrest. *Circ J*. 2016;80:2124-2132
22. Guerci AD, Shi AY, Levin H, Tsitlik J, Weisfeldt ML, Chandra N. Transmission of intrathoracic pressure to the intracranial space during cardiopulmonary resuscitation in dogs. *Circ Res*. 1985;56:20-30
23. Yannopoulos D, Aufderheide TP, Abella BS, Duval S, Frascone RJ, Goodloe JM, Mahoney BD, Nadkarni VM, Halperin HR, O'Connor R, Idris AH, Becker LB, Pepe PE. Quality of cpr: An important effect modifier in cardiac arrest clinical outcomes and intervention effectiveness trials. *Resuscitation*. 2015;94:106-113
24. Debaty G, Lurie K, Metzger A, Lick M, Bartos JA, Rees JN, McKnite S, Puertas L, Pepe P, Fowler R, Yannopoulos D. Reperfusion injury protection during basic life support improves circulation and survival outcomes in a porcine model of prolonged cardiac arrest. *Resuscitation*. 2016;105:29-35
25. Matsuura TR, Bartos JA, Tsangaris A, Shekar KC, Olson MD, Riess ML, Bienengraeber M, Aufderheide TP, Neumar RW, Rees JN, McKnite SH,

Dikalova AE, Dikalov SI, Douglas HF, Yannopoulos D. Early effects of prolonged cardiac arrest and ischemic postconditioning during cardiopulmonary resuscitation on cardiac and brain mitochondrial function in pigs. *Resuscitation*. 2017;116:8-15

26. Halperin HR, Lee K, Zviman M, Illindala U, Lardo A, Kolandaivelu A, Paradis NA. Outcomes from low versus high-flow cardiopulmonary resuscitation in a swine model of cardiac arrest. *Am J Emerg Med*. 2010;28:195-202
27. Pantazopoulos IN, Xanthos TT, Vlachos I, Troupis G, Kotsiomitis E, Johnson E, Papalois A, Skandalakis P. Use of the impedance threshold device improves survival rate and neurological outcome in a swine model of asphyxial cardiac arrest*. *Crit Care Med*. 2012;40:861-868